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Clinical Impact of Proton Pump Inhibitors on the Action of Aspirin

Meenaaz Fatima

Department of Pharmacy Practice, Shadan College of Pharmacy, Hyderabad, Telangana, India

Abstract: ***Aspirin is the most potent drug with widespread use. It exist anti-inflammatory, anti-pyretic and well defined anti-platelet activity. Low-dose aspirin is commonly used for cardiovascular and cerebro-vascular diseases. Treatment and prevention of cardiovascular events require long term use of low-dose aspirin. However, long term use of aspirin is associated with major adverse effects of gastro-intestinal bleeding. This may results in non-adherence of aspirin leading high rate of mortality. To prevent this, clinical guidelines recommended the use of proton pump inhibitors as a co-therapy with aspirin. Being a gastro-protective, it is mainly prescribed for the secondary prevention of aspirin-induced bleeding. It exerts its action by suppressing the gastric acid secretion and altering the gastric P^H. Aspirin, which is a weak organic acid, requires the acidic medium for better absorption. Co-therapy with proton pump inhibitors reduces the absorption of aspirin. Thus, proton pump inhibitors attenuate the anti-platelet effect of aspirin. However, many researchers do not support this data and suggest use of proton pump inhibitors is considered to be safe and effective. Many studies do not report any clinical evidence of such interaction except the few. Thus, clinical guidelines encouraged for further investigation regarding such interaction for better clinical impact in future. Till then proton pump inhibitors can be practised safely and effectively in aspirin users. Moreover, it suggest for the appropriate selection of proton pump inhibitors. Selection of proton pump inhibitors should be based on the risk-benefit ratio. It must be prescribed only to the patients who are at high risk of gastro-intestinal bleeding. Further studies have to be conducted to evaluate the drug interaction really exist or not. The current article reviews and summarizes the clinical impact of proton pump inhibitors in long term aspirin users.***

Keywords: low-dose aspirin, proton pump inhibitors, H_2 receptor blocker; gastrointestinal bleeding; major adverse cardiovascular events.

Abbreviations:
PPIs: proton pump inhibitors; GIT: gastrointestinal tract; CVS: cardiovascular system
LDA: low dose aspirin; ST: Stent thrombosis; MACE: major adverse cardiac events
DAPT: dual anti-platelet therapy; PCI: percutaneous coronary intervention

1. Objective

The main objective of this article is to know the effect of aspirin and proton pump inhibitors when used concomitantly in patients with cardiovascular diseases. This article also reviews the beneficial and adverse effects of these drugs on the cardiovascular and gastrointestinal system. It also summarizes the mechanism by which the protons pump inhibitors effects the efficacy of aspirin. It also evaluates the clinical impact of concomitant use of PPIs and aspirin in cardiovascular diseased patients. We will also discuss the new strategies to overcome the adverse effects caused by the use of these drugs when used concomitantly.

2. Methods

Various articles which were published in PubMed, Google Scholar, Med Line, Web of Science and Crossref during the period of 2010-2019 were reviewed and assessed carefully. Articles includes: systematic review articles, retrospective, cohort study, meta-analysis, case-control study and various other research articles. Articles with irrelevant data were excluded in this study.

3. Introduction

Aspirin is commonly used as anti-pyretic, analgesic agent. Low doses of aspirin act as anti-platelet used to prevent blood clot. It is commonly prescribed drug by many physician to prevent the cardiovascular events. Proton pump inhibitors are commonlyused to prevent acidity, peptic ulcer disease. PPIs are also prescribed in order to prevent GI upset caused by polypharmacy.

Patients with cardiovascular diseases require long term therapy of aspirin with or without clopidogrel. However, long term use of aspirin may result in gastrointestinal bleeding, gastric ulcers or haemorrhage. In order to prevent these complications, proton pump inhibitors were prescribed.

A new guideline according to the American Heart Association(AHA) and the American College of Cardiology (ACC) suggest that the aspirin therapy which is commonly used for primary prevention of heart attack in older people over 70 years who are not currently suffering from heart disease is non beneficial. Further increases the risk of bleeding in GIT and rarely in brain.[1]

Thus, a cohort study which was carried out in 2017 interpretate that there is the higher risk of GI bleeding associated with long term aspirin in patients over 75 years. Co-therapy with PPIs can be consider as heal up therapy for such aspirin-induced bleeds.[2]

a) Clinical Evidences

A recent study suggested that they might be a potential drug interaction between PPIs and aspirin but due to the limited studies on this interaction, does not come to the conclusion. As there is a need for further research, meanwhile PPIs can

still prescribe to prevent GI bleeding caused by aspirin. However, this drug interaction can't be completely excluded. So there is a need to stress on the further studies to investigate whether concomitant use of aspirin and PPIs causes clinical attenuation of the anti-platelet effect of aspirin.[3]

Another analysis was carried out which provide the evidence that the aspirin plus PPIs co-therapy shows better outcome with fewer side-effects when compare to aspirin alone (7.2% VS 3.4%) and increased aspirin adherence (74% VS 71%) which results in fewer recurrent MIs (26 fewer events per 10,000 patients). However further investigation is required regarding the safety of this co-therapy.[4]

Moreover, aspirin treated patient dissuade by the US Federal Drug Administration's and European medicines Agency's for the use of PPIs. However, many American college of cardiology follows the clinical practice guidelines recommendations. Hence, it remain the controversy for the use of PPIs in aspirin treated patients.[5]

A case control study was carried out by M.Wurtz and EL. Grove to evaluate the effect of PPIs on the platelet response to aspirin in 418 stable patients with CAD, of whom 54 were treated with PPIs and platelet aggregation was measured and concluded that patients with CAD treated with PPIs had a reduced platelet response to aspirin compared with patients who were not treated with PPIs and reported that co-therapy of aspirin and PPIs might lower the cardio protective effect of aspirin.[6]

In 2018, a meta-analysis was carried out in large number of patients taking aspirin and PPIs to evaluate the adverse reaction concerned with the co-therapy of aspirin and PPIs and concluded that there is an increased rates of major adverse cardiovascular events, stent thrombosis (ST) and revascularization in patients taking aspirin with PPIs when compared to those who are taking aspirin alone.[7]

A retrospective cohort study suggested that there is an increased risk of Major Adverse Cardiovascular Events in patients taking anti-platelet therapy with PPIs when compared to without PPIs users in Chinese patients.The US FDA highlights the need for further investigations to evaluate clinical safety of anti-platelet agents when used concomitantly with a PPI as several clinical trials suggested that this interaction occur rarely and can be prescribe clinically.[8]

b) Mechanism

Since, it is the major concern for the use of PPIS and aspirin concomitant in cardiovascular diseased patients. Hence, it is important to know the mechanism by which these drugs interact with each other. As we all know low dose aspirin exhibit cardioprotective effect due to its anti-platelet property, it is commonly prescribed to CAD patients. Long term use of aspirin is associated with GI bleeding. To prevent this, clinical guidelines recommends PPIs. Since, aspirin is an acid, it shows better absorption in acidic medium. Use of PPIs lowers the gastric acid and might interfere with the absorption of aspirin. Thus, the anti-platelet property of aspirin might be diminished leading to increased risk of cardiovascular events.

Lets us see the exact mechanism of PPIs and aspirin to understand the interaction between them.

- **Mechanism of PPIs**

H^+, K^+-ATPase, a membrane bound proton pump in the gastric parietal cells, which secretes the intragastrichydrochloric acid responsible for the gastric acid microenvironment. When these parietal cells get activated, proton pump translocate from tubulovesicles to the membrane of secretory caniliculi. PPIs mainly inhibit this H^+, K^+-ATPase. Thus interfere with gastric acid secretion. Being a lipophillic drug, they are inactive in the neutral environment. After the absorption, they get deposited in the secretory canaliculi of gastric parietal cells, get protonated and then transform into active form which react covalently with the cysteine sulfhydryl group of proton pump, inactivate it and inhibit the gastric acid secretion. PPIs are very specific as they gets activated only in stomach acidic environment.[9]

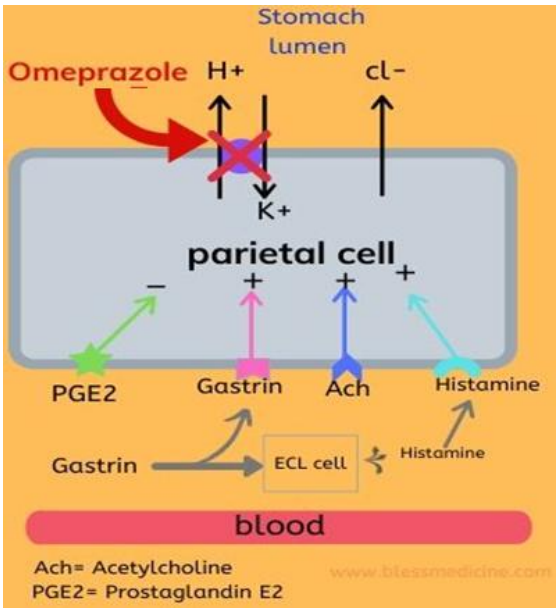

Figure 1: Mechanism of proton pump inhibitors

- **Mechanism of aspirin**

Though aspirin exhibit different mechanisms for its different pharmacological action, let us focus on its anti-platelet action. Low dose aspirin (LDA: 75-100 mg/day) is usually prescribed to treat thrombosis, stroke and other cardiovascular events. LDA irreversibly acetylate serine 530 of enzyme COX-1, thus inhibiting the synthesis of thromboxane-A_2, thus exhibiting anti-thrombotic effect.[10]

Although the mechanism and site of action of both the drugs are different, lets us have a look on the pharmacology of aspirin to understand how the PPIs affect the efficiency of aspirin.

- **Pharmacology of aspirin**

Aspirin is well absorbed in the acidic microenvironment in its non-ionized lipid state across gastric mucosal barrier. At this state, aspirin inhibits the gastro-protective prostaglandin

synthesis. Thus, long term use of aspirin used to prevent cardiovascular events might be associated with gastric bleeding. In the acidic medium, carboxylic acid residue of aspirin gets protonated and reduces the rate of hydrolysis. When it enters into the alkaline medium of gastroduodenum, carboxylic acid gets deprotonated and increase the rate of hydrolysis and transacetylation. Half-life of single oral dose of aspirin is 13-19 min and IV aspirin has 3 min of half-life.[11]

- **Mechanism of Potential drug interaction**

Since, PPIs inhibits the H^+,K+ ATPase pump and interferes with gastric acid secretion which lead to increase in the intragastric P^H above the pK_a (3.5) of aspirin causing marked reduction in lipophilicity of aspirin. Thus, retarding its absorption.[3]

Another mechanism explained that PPIs interferes with the activity of nitric oxide synthase enzyme. This enzyme is mainly involved in vascular homeostasis. It helps in vasodilation and inhibits the platelet aggregation. Thus, PPIs increases the risk of cardiovascular events.[12]

Moreover, another drug clopidogrel which used as anti-platelet agent to prevent the cardiovascular event also known to interact with the long term use of PPIs. Enzyme CYP2C19 is essential for the activation of clopidogrel. Patients on clopidogrel using PPIs may alter the anti-thrombotic activity and increase the risk for cardiovascular events.[13]

There are some reports investigated by researchers suggesting that PPIs reduces clopidogrel activity by inhibiting the enzyme CYP2C19 which is essential for the activation of clopidogrel.[14]

c) Strategies for Better Clinical Impact

Most of the patients with cardiovascular diseases wereprescribed with Dual Anti-Platelet Therapy DAPT (CLOPIDOGREL+ ASPIRIN) which shows better clinical outcome as clopidogrelcompensate the incomplete absorption of aspirin which is caused by PPIs used for secondary prevention of GI bleeding caused by long term use of aspirin.

Enteric coated aspirin reduces the bleeding effects in GIT. This formulation also increases the rate of absorption and delays its metabolism and activity.[11]

However, a clinical trial which was carried out in the year 2017 reported that several patients with diabetes receiving enteric coated aspirin shows partial inhibition of thromboxane B_2 due to insufficient absorption which leads to aspirin resistance showing that enteric coated aspirin tablets exhibit poor response.[15]

Some studies suggest that rabeprazole does not deteriorate the anti-thrombotic activity of clopidogrel as rabeprazole is not mainly metabolized by the enzyme CYP2C19.[13]

As pantoprazole and lansoprazole are the metabolism-independent inhibitors of CYP2C19, shows least interaction with clopidogrel. Hence can be prescribed for the secondary prevention of gastro-intestinal bleeding to patients on clopidogrel. However, omeprazole and esomeprazole are the irreversible metabolism-dependent inhibitors of CYP2C19, they must not be given concomitantly with clopidogrel in patients who are at high risk of GI bleeding.[14]

Moreover, in the large cohort of propensity score analysis reported that the co-therapy of PPIs and DAPT is not associated with increased risk of MACE in patients who had undergone percutaneous coronary intervention (PCI) at up to 2 years of follow-up.[16]

In 2009, Dr.S T Ali and co-authors suggested in their paper that famotidine, a H_2 receptor antagonist can be considered as the alternative to PPIs in patients with long term use of aspirin for vascular protection.[17]

Another Phase 3, randomized double-blind trial reports that famotidine shows 80% deduction in gastric ulcer in patients with cardiovascular disorders.[18]

A comparative study was carried to evaluate the efficacy of PPIs (omeprazole) and H_2 blocker (famotidine) in patients with long term aspirin users and suggested that omeprazole shows better clinical outcome in reducing the aspirin-induced ulcers when compared to famotidine. However, similar risk for thromboembolic events was reported for both the drugs in this cohort study.[19]

Another study reports superiority of PPIs over H_2 receptor blockers in long term aspirin users for the risk of recurrent GI bleeding.[20]

A clinical trial concluded that PA32540, a coordinated delivery tablet with aspirin core whose coating dissolves in a $P^H > 5.5$ surrounded by immediate release omeprazole passes phase 1 and phase III trial suggesting omeprazole does not interfere with the anti-platelet effect of aspirin and shows the promising results.[21]

Even though, clinical guidelines strongly recommends PPIs for the secondary prevention of gastrointestinal bleeding caused by long term use of aspirin, there is huge controversy regarding the concomitant use of anti-platelet drug and PPIs. Due lack of sufficient data regarding this drug interaction, there is an urgent need for further studies and clinical evidence to evaluate the clinical outcome.

However, PPIs is considered to be the potent drug to prevent GI bleeding and gives the better clinical outcome. Many studies provide the clinical evidence that such interaction does not exist in most of the cases, hence it is safe to consider PPIs in patients with long term aspirin. But such interaction which was reported in some cases can't be neglected. Extreme caution should be taken while prescribing these medications.

4. Author's Opinion

Selection of PPIs should be based on risk-benefit ratio.

Patients who are at low risk of GI bleeding, Use of PPIs can be avoided.

Patients with poor CYP2C19 metabolising activity should not be prescribed with PPIs

PPIs should be selected which are appropriate and safer generation.

Dual Anti-Platelet therapy (clopidogrel + aspirin) shows better clinical impact when compared to aspirin alone.

Cardiovascular functioning should be monitored closely when proton pump inhibitors and anti-platelet therapy was prescribed concomitantly

5. Conclusion

There are lot of controversies regarding the attenuation of anti-platelet activity by PPIs. Since, clear evidence is not present till now, clinical guidelines recommends the use of PPIs in aspirin users as it provide better clinical outcome. Of course, this interaction can't be neglected. Care has to be taken regarding the potential risk during the course of therapy. As there is an insufficient data exist regarding the interaction between PPIs and Anti-platelet drug further investigation need be carried out.

Conflicts of Interest: Nil

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